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Short Report

Screening of hepatitis E in patients presenting for acute neurological disorders

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ABSTRACT

Introduction: Hepatitis E virus (HEV) infection has been reported to be associated with neurological disorders. However, the real prevalence of acute hepatitis E in those diseases is still unknown. We determined the prevalence of anti-HEV IgM antibody in a population with acute non-traumatic, non-metabolic, non-vascular neurological injury.

Method: A registry was created in Grenoble Hospital University from 2014 to 2018 to collect data on patients with acute (<3 months) non-traumatic, non-metabolic, non-vascular neurological injuries. Acute hepatitis E was defined as anti-HEV IgM-positive serum in immunocompetent patient, and as anti-HEV IgM-positive serum or HEV RNA-positive serum in immunocompromised patients.

Results: One hundred fifty-nine patients were included. Anti-HEV IgM seroprevalence in our cohort of non-traumatic, non-metabolic, non-vascular neurological injuries was 6.9% (eleven patients, including 4 Parsonage–Turner syndrome (PTS) and 2 Guillain–Barré syndrome (GBS)). Elevated transaminases were observed in only 64% of hepatitis E patients and cholestasis in 64%.

Conclusion: In this study, 6.9% of patients with acute non-traumatic, non-metabolic, non-vascular neurological injuries had a probable recent HEV infection. HEV serology should be systematically performed in this population, even in patients with normal transaminase level.

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Introduction

HEV infection has been reported to be associated with many different acute neurological disorders, especially inflammatory ones [1]. Indeed, over 100 cases have been described, including both central nervous system diseases (such as encephalitis or myelitis) and peripheral neurological diseases (such as Guillain–Barré syndrome (GBS), Parsonage–Turner syndrome (PTS)) [1]. Kamar et al. recommend to treat these disorders when there are associated with HEV with Ribavirin, an anti-viral agent [2]. However, none study has already addressed the question of HEV prevalence among neurological disorders. Because of the suspected immunological underlying mechanism, we proposed to study the prevalence of acute hepatitis E in acute non-traumatic, non-vascular, non-metabolic neurological injuries among a French monocentric cohort.

Material and methods

A registry was created in Grenoble Hospital University from 2014 to 2018 to prospectively collect data on patients with acute (<3 months) non-traumatic, non-metabolic, non-vascular neurological injuries. A case of acute hepatitis E was defined as positive serum anti-HEV IgM (using Assure HEV IgM Rapid test (MP Biomedicals)) in immunocompetent patient and as positive serum anti-HEV IgM or positive serum HEV RNA in immunocompromised patients [3].

When available, serum HEV RNA was done to confirm acute HEV infection (using Ceeramtools® Real-time reverse transcription polymerase chain reaction (PCR) kits, Ceeram SAS).

Statistical analysis

Continuous variables were compared using the non-parametric Wilcoxon test. Categorical variables were compared using the Chi square test (if number of patients was >5 patients) or using the Student test. All tests were two-sided. $p < 0.05$ was considered to be significant.

Case reports

From 2014 to 2018, we prospectively included 159 patients (median age 57 [19–92], 66 females). Written consents from all patients were collected.

Results of anti-HEV IgM assay were positive for 11 patients (6.9%) and equivocal for three patients. Among them, five had positive HEV RNA identified in serum (BankIt2288249Gre-143251634.MN747090, BankIt2288249Gre-170663087.MN747091, BankIt2288249Gre-172652224.MN747092, BankIt2288249Gre-172652258.MN747093, BankIt2288249Gre-181722177.MN747094).

Anti-HEV IgM were statistically more frequent among patients with increased transaminase level (AST > 37 IU/L for and ALT > 78 IU/L) (7/47 in patients with transaminase level increment versus 4/107 in patients with normal transaminase level, odds ratio (OR): 4.46, 95% CI 1.07–21.9; $p = 0.035$). Likewise, anti-HEV IgM were more frequent in patients with cholestasis (bilirubin > 17 $\mu\text{mol/L}$, ALP > 117 IU/L, GGT > 85 IU/L) than in patients without cholestasis (7/11 in HEV-, 33/136 in non-HEV patients, OR: 5.38, 95% CI 1.28–26.7, $p = 0.01$). Quantitative value of AST, ALT and ALP did not differ ($p = 0.64$, 0.37 and 0.83 respectively).

Neurological injuries associated with possible acute HEV infection were miscellaneous: PTS ($n = 4$); GBS ($n = 2$), meningoencephalitis ($n = 2$), meningoradiculitis ($n = 1$), paresthesia ($n = 1$) and a facial paralysis associated with paresthesia ($n = 1$) (Table 1). Among them, three cases had other infections (one with varicella-

Table 1

Type of acute neurological event.

Type of acute neurological event (No)	All patients (159)	HEV patients (11)
Central	71	2
Encephalitis	43	2 ^a
Infectious	22	
HSV	5	
VZV	2	
Influenzae	2	
HHV6	1	
EBV + <i>Mycoplasma pneumonia</i>	1	
<i>Bartonella henselae</i>	2	
<i>Neisseria meningitis</i>	2	
<i>Listeria monocytogenes</i>	1	
<i>Streptococcus pneumoniae</i>	2	
<i>Streptococcus dysgalactiae</i>	1	
<i>Staphylococcus aureus</i>	1	
Cysticerci	1	
<i>Plasmodium falciparum</i>	1	
Dysimmune	6	
GAD-65 Ab	1	
GABA-R Ab	1	
Atypical Ab	1	
Hashimoto encephalitis	1	
No Ab	2	
Unknown	15	
Myelitis ^b	8	
Multiple sclerosis	13	
NMO	1	
Lyme myeloradiculitis	1	
Pachymeningitis	3	
Unknown	2	
Peripheral	79	9
Typical GBS	45	2
MFS	5	
Bickerstaff syndrome	1	
Meningoradiculitis	4	1
Multiple mononeuropathy	3	
Atypical facial palsy ^c	6	1
PTS	7	4
CIDP	2	
Axonal sensory neuropathy	1	
Small fiber neuropathy	1	
Ataxic neuropathy	1	
Painless sensory disorders	3	1
Myasthenia	9	

HSV: herpes simplex virus; VZV: varicella zoster virus; HHV6: human herpesvirus type 6; EBV: Epstein Barr virus; GAD-65: glutamic acid decarboxylase 65; Ab: antibodies; GABA-R: γ -aminobutyric acid; NMO: neuromyelitis optica; GBS: Guillain–Barré syndrome; MFS: Miller-Fisher syndrome; PTS: Parsonage–Turner syndrome; CIDP: Chronic inflammatory demyelinating polyneuropathy.

^a Two cases of presence of positive HEV and another infection.

^b Myelitis secondary to Multiple Sclerosis were not included in this section.

^c 2 patients with bilateral facial palsy, 1 with unilateral facial palsy associated with vestibular syndrome and 3 with unilateral facial palsy associated with paresthesia.

zoster virus, one with *Listeria monocytogenes* and one with cytomegalovirus (CMV) infection). In these cases, serum HEV RNA were negative (Table 2).

Discussion

Our study demonstrates a high prevalence (6.9%) of positive anti-HEV IgM in our cohort of acute non-traumatic, non-vascular neurological injury compared to anti-HEV IgM seroprevalence in Iseré's blood-donor (0.4% 95% CI 0.01–2.3) at the same period of time [4].

In our population with possible acute hepatitis E, three different syndromes were predominant: PTS, GBS and encephalitis.

More than half of the PTS patients (57%) had positive anti-HEV IgM. Unlike typical PTS, patient with HEV often presented bilateral neuralgia ($p < 0.0001$), as it was described before [5]. We reported

Table 2
Clinical and laboratory features of possible acute HEV patients.

Patient No.	Sex/ Age at onset y	Neurological disorder	Season at the onset	Warning signs	Liver enzymes ^a		Co-diagnosis	HEV	HEV			Treatment	Sequelae	Follow up times (week)
					Cytolysis	Cholestasis			Serum PCR	CSF PCR	Stool PCR			
1	M/50	PTS	spring	No	1.5 N	3 N	No	-	-	-	NA	No	PTS	8
2	F/43	PTS	summer	flu like	2N	3 N	No	+	NA	+	3f	No	PTS	3
3	F/34	Atypical FP	spring	flu like	No	No	No	-	-	-	NA	No	FP	2
4	F/83	GBS	summer	diarrhea	1.5 N	1.5 N	No	+	NA	NA	3h	IV Ig	GBS	7
5	F/49	Painless sensory disorders	summer	No	No	1.5 N	No	-	NA	NA	NA	No	Paresthesia	18
6	M/75	ME	autumn	No	No	No	Listeria	-	NA	NA	NA	No	No	3
7	M/58	PTS	autumn	myalgia	5 N	4 N	No	-	NA	NA	3c	IV Ig	PTS	17
8	F/20	GBS	winter	flu like	2 N	No	CMV	+	NA	NA	NA	IV Ig+ACV	No	16
9	M/34	MR	summer	diarrhea	9 N	1.5 N	No	+	NA	+	3f	No	No	1
10	M/80	ME	autumn	No	No	8 N	VZV	-	NA	NA	NA	ACV	No	1
11	M/38	PTS	summer	flu like	28 N	8 N	No	+	NA	NA	3f	CT	PTS	2

HEV: hepatitis E virus; M : male; F : female; y : Year; bilirubin normal range 3–17 µmol/l; AST (aspartate aminotransferase) normal range <37 IU/L; ALT (alanine aminotransferase) normal range <78 IU/L; ALP (alkaline phosphatase) normal range 45–117 IU/L; GGT (gamma glutamyl transferase) normal range 15–85 IU/L; WBC: white blood count; CSF: cerebrospinal fluid; y: year; CMV: cytomegalovirus; VZV: varicella-zona virus; PTS: Parsonage–Turner syndrome; GBS: Guillain–Barré syndrome; ME: meningoencephalitis; FP: nerve facial paralysis; MR: meningoradiculitis; PCR: polymerase chain reaction; GT: genotype; IV Ig: intravenous immunoglobulin; ACV: acyclovir; NA: not available; N: normal value.

^a Results were expressed in times greater than normal if elevated liver enzyme was present.

two cases with phrenic damage or limb manifestation. These features had also been described before [5].

Among the 45 patients with GBS, two had positive anti-HEV IgM serology (4.4%). GBS is known to be triggered by some infection such as CMV [6]. HEV could be another trigger. Thus, in the literature, more than 50 cases of GBS were described associated with HEV [6]. In our study, one of the two patients with GBS had, concomitantly with positive HEV IgM serology, an acute CMV infection: this raises the question of the real underlying role of HEV in this case. Few cases of cross-occurrence of CMV and HEV have been described before [7]. Because of the known cross-reactivity with EBV (which is described in the manufacturer's instructions for Mikrogen recomLine HEV IgG/IgM test), cross-reactivity between CMV and HEV should be considered.

The question of cross-reactivity is raised in 2 described HEV patients with meningoencephalitis. Indeed, these two cases had other infections (one varicella-zoster virus (VZV) and one *Listeria monocytogenes*). Diagnosis of HEV, according to the French recommendations [3], was done in this study by positive HEV IgM serology with the use of IgM rapid test. Various commercially available serological anti-HEV diagnostic tests currently exist. All of them are very sensitive (from 85% to 94%) [8]. Instead of a high sensitivity of all these methods, important differences in the performance between them have been observed [8,9]. Recently, Vollmer et al. [8] have found that MP-Bio assay has a higher sensitivity than Wantai or Mikrogen assay, but a smaller positive post-infection period. Neurological manifestations after acute hepatitis E may appear a few months after infection [2]. For that reason and because of possible cross-reactivity [7,10], interpretation of HEV serology assay should be considered with caution. Blood PCR seems to be more specific however its period of positive testing is shorter [2,9].

In our study, other neurological patterns have been found, like atypical facial nerve palsy (1) or meningoradiculitis (1) or painful sensory disorder (1). Those entities were also previously described in association with hepatitis E [11,12].

A liver enzyme increment was found more frequently in patients with positive anti-HEV IgM. This underlines the fact that the acute HEV infection is often but not systematically associated with liver enzyme modification.

This current study has several limitations, among them, the small sample size and the absence of control group.

Conclusion

This prospective monocentric study highlighted a high probability (6.9%) of HEV acute infection. In acute non-traumatic, non-metabolic, non-vascular neurological injuries (especially GBS, PTS and encephalitis); a causal relationship between HEV and such neurological disorders is possible. This study contributes to identify of subpopulation in which ribavirin therapeutic trial could be investigated.

Author contributions

Wrote the first draft of the manuscript: AB. Contributed to the writing of the manuscript: AB, AV, AD, FSR, BC, AB, IBG, CW, ML, MD, ML, VL, MM, RCM, DVDV, MV, EL, OE, CDP, JL, SL, PM, CS, JLB, LB. ICMJE criteria for authorship read and met: AB, AV, AD, FSR, BC, AB, IBG, JL, CW, ML, VL, MM, RCM, DVDV, PD, ML, MV, EL, OE, CDP, JL, SL, PM, CS, JLB, LB. Agree with manuscript results and conclusions: AB, AV, AD, FSR, BC, AB, IBG, CW, ML, PD, ML, VL, MM, RCM, DVDV, MV, EL, OE, CDP, JL, SL, PM, CS, JLB, LB.

Laurence Bouillet had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Collaborators

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Competing interests

None declared.

Ethical approval

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